DRP2/dystroglycan complex. Periaxin and DRP2 are specifically present or highly enriched in myelin-forming Schwann cells, respectively, and DRP2 has thus far been shown to interact with dystroglycan only in Schwann cells. Hence, the complex is an appropriate candidate for a Schwann cell-specific function.

The late onset of demyelination and the particular combination of pathological features of the periaxin null mouse suggest that the periaxin/DRP2/dystroglycan complex serves to maintain myelin. Interestingly, this hypothesis taken together with the association between periaxin mutations and hereditary demyelinating neuropathies predict that other components of the periaxin assembly could provide additional candidate genes. One obvious choice is *DRP2* itself, located at Xq22.1 (Roberts, 2001), near a locus for an X-linked Charcot-Marie-Tooth neuropathy not yet molecularly identified.

A maintenance role could be effected by either mechanical means—in muscle the dystrophin/dystroglycan complex is thought to buffer mechanical stress—or through signaling. The authors speculate that a periaxin/DRP2/dystroglycan complex could transduce signals that regulate myelin sheath thickness and thus stability. For example, in muscle, syntrophins contain PDZ domains and are thought to be adaptors that recruit a variety of signaling molecules to the dystrophin/dystroglycan assembly (Roberts, 2001). In addition, ectopic expression in muscle of mutant dystrophins that can not bind dystroglycan can partially rescue the muscular dystrophy phenotype, suggesting that dystrophins themselves may transduce signals (Rafael et al., 2000). In this context, it is notable that DRP2 has a unique amino terminus with unknown function. Finally, dystroglycan can also recruit adaptors typically associated with signal transduction.

What about a more general role in myelination? Certainly the phenotype of dystrophic (*dy/dy*) mouse suggests that laminin mutations have their effect prior to and during myelinogenesis (Bunge, 1992), suggesting as one possible mediator the periaxin/DRP2/dystroglycan assembly. It could simply subserve the demanding architectural problem of myelinogenesis by linking laminin in the basal lamina to the cytoskeleton. Or it could play a role in signaling; laminin and basal lamina assembly are thought to regulate myelin gene expression, for example (see references in Sherman et al., 2001). An important question is when interaction begins in developing nerve. Periaxin is present before birth, DRP2 at least by 10 days after birth (this study), and dystroglycan perinatally. One interesting observation from this study is that the basic domain of periaxin is required for DRP2 binding. This same domain acts as a nuclear localization signal in embryonic Schwann cells. Then periaxin relocates to the cytoplasm of Schwann cells perinatally just prior to myelination—does DRP2 appear at this time and mask the nuclear localization signal? In addition to expression analysis, ongoing studies to disrupt the genes encoding DRP2 and dystroglycan either singly or doubly in the presence or absence of periaxin will better define a role in myelin formation and maintenance. A tantalizing hypothesis is that this complex appears and alters the cytoskeletal linkage at the time when Schwann cells have exited from the cell cycle, and begin to form myelin. Or as firemen instruct schoolchildren, Schwann cells may stop, DR(o)P2, and roll.

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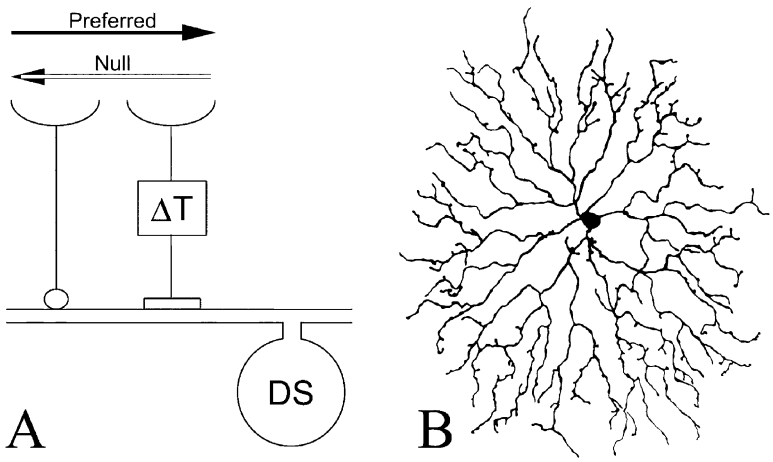
Knock Out of Direction Selectivity in the Retina

Retinal ganglion cells show direction selectivity in their responses to moving stimuli. The circuitry necessary to generate directional selectivity in these cells has been long debated. Yoshida et al. (2001) use immunotoxin-mediated cell ablation to demonstrate that the starburst amacrine cell is at the core of this computation.

Visual motion detection is a classical problem of computational neuroscience. Despite many efforts during the last 40 years, we still do not understand the synaptic connectivity and signaling that result in direction selectivity (DS) in retinal ganglion cells. According to the model proposed by Barlow and Levick (1965), each ganglion cell receives signals derived from two neighboring image locations, one excitatory and one inhibitory (see figure, panel A). The inhibitory input is displaced toward the preferred direction of the ganglion cell and, in addition, is delayed. Thus, a stimulus moving in the null



Schematic of Components Required to Generate a Directionally Selective Response in Retinal Ganglion Cells

(A) Model of a direction selective (DS) ganglion cell as proposed by Barlow and Levick (1965). A small part (a subunit) of the dendritic field of the DS cell is shown. It receives input from two neighboring image locations (left: excitatory, right: inhibitory). The inhibitory input is delayed (ΔT).

(B) Starburst amacrine cell of the mouse retina (dendritic field diameter: 200 μm, intracellularly injected with Lucifer Yellow, from Wässle and Boycott, 1991).

direction would drive inhibition of the postsynaptic cell and shunt the subsequent excitatory input, while movement in the preferred direction would result in a delayed and therefore ineffective inhibitory input leading to net excitation of the postsynaptic cell.

One recent study of whole-cell recordings from rabbit DS ganglion cells supports this "postsynaptic" model (Taylor et al., 2000), while another examining DS ganglion cells of the turtle retina suggests that cells "presynaptic" to ganglion cells already exhibit DS light responses (Borg-Graham, 2001). One set of presynaptic cells that might play a role in the DS response is the cholinergic amacrine cells, called "starburst" amacrine cells (see figure, panel B) because of their regularly spaced, evenly radiating dendrites (Famiglietti, 1991). They are found in all mammalian retinae (Wässle and Boycott, 1991), occur in relatively high density, and their dendrites costratify and cofasciculate with the dendrites of DS ganglion cells. In an elegant experiment, He and Masland (1997) recorded from DS ganglion cells of the in vitro rabbit retina before and after partial removal by targeted laser ablation of starburst cells surrounding the recorded DS ganglion cell. While the overall responsiveness of the ganglion cell decreased on ablation of starburst cells, the DS light responses persisted, suggesting that starburst cells provide a substantial input to the response of ganglion cells to moving stimuli but do not participate in the DS response.

In the current issue of *Neuron,* Yoshida et al. (2001) present exciting new data to propose instead a prominent role of starburst amacrine cells in the generation of DS light responses. The different result is due to the use of a different method that results in more complete cell ablation. Since starburst amacrine cells express the metabotropic glutamate receptor type 2 (mGluR2; Koulen et al., 1996), these investigators used the mGluR2 promoter to drive the selective expression of green fluorescent protein (GFP) fused to the human interleukin 2 receptor α-subunit (hIL-2Rα) in these cells in transgenic mice. Microinjection into the eye of a monoclonal hIL-2Rα antibody fused to a bacterial toxin then resulted in specific ablation of only the starburst cells. Two weeks after the immunotoxin injection, 90% of the starburst cells were gone, and extracellular recordings from retinal ganglion cells showed no DS response in ganglion cells. In addition, Yoshida et al. (2001) demonstrate that, while optokinetic nystagmus (OKN, a stereotyped visuomotor reflex induced by a moving stimulus) could be elicited from wild-type mice, ablation by immunotoxin of starburst cells in transgenic mice eliminated this response.

One might argue that ablation of starburst cells only deprived DS ganglion cells of their excitatory cholinergic drive and thus silenced the cells. However, as has been shown by He and Masland (1997), blocking the cholinergic drive by d-tubocurarine reduces the total response of DS cells by only 50%, because they also receive excitatory input from bipolar cells through glutamate receptors. Hence, ablation of starburst cells appears to interfere directly with the generation of DS light responses of the ganglion cells; starburst cells appear to be the key player.

Starburst cells have some unique characteristics that may explain their complex role in generation of the DS ganglion cell response. They receive synaptic input along the whole length of their dendrites, but their outputs to retinal ganglion cells are restricted to the distal third of their dendrites, leading to an asymmetric relationship between input and output (Famiglietti, 1991). Because of this asymmetry, and because starburst cells release both excitatory acetylcholine and inhibitory GABA (O'Malley et al., 1992), it was proposed that they selectively excite ganglion cells when a light stimulus moves in the preferred direction and inhibit ganglion cells when the stimulus moves in the null direction (Vaney, 1991). There is common agreement that GABA is the inhibitory transmitter responsible for inhibition in the null direction, because DS is abolished by the GABA antagonist picrotoxin (Ariel and Daw, 1982). The excitatory input to the DS ganglion cells is less clear, although there is good evidence for a contribution from cholinergic starburst amacrine cells (He and Masland, 1997).

It will be a real challenge for future work to reveal the synaptic details of how starburst cells are involved with DS ganglion cells. Immunocytochemical markers have shown that starburst cells express unusual synapse-associated proteins suggesting unique mechanisms of releasing their two transmitters, GABA and acetylcholine. They also express special sets of glutamate and GABA receptors (Brandstätter et al., 1995). The model in

the figure (panel A) describes the minimum requirements for the DS response, which are a spatial asymmetry and a time delay between the excitatory and inhibitory synapses. Yoshida et al. (2001) demonstrate that the starburst cell may contribute to both of these minimum requirements. However, one can predict that we have to understand much more of the molecular and synaptic details of the starburst cell circuitry before directional selectivity, this classical problem of computational neuroscience, is finally understood.

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Reverse Spikeology: Predicting Single Spikes

Neural models that simulate single spike trains can help us understand the basic principles of neural coding in vision. Keat et al. (2001) develop a hybrid model that combines spatiotemporal filtering with nonlinear spike generation. The model does a good job of predicting the responses of single retinal ganglion cells and thalamic relay neurons.

When a digital camera is used to capture an image, the camera converts the analog luminance signal into a binary series of zeros and ones. Given only this binary signal and no information about the coding process, it would be difficult for an observer to reconstruct the original image. A similar coding process happens in the brain when analog signals in the retina are recoded by retinal ganglion cells into action potentials. From that point onward, neurons throughout the visual system represent the world in terms of time varying spike trains. Understanding these neural codes is one of the central goals of systems neuroscience. The report by Keat et al. (2001 [this issue of *Neuron*]) addresses this issue by modeling how early visual neurons translate stimuli into spikes.

To investigate neural coding, many researchers have used computational tools adopted from linear systems analysis (Marmarelis and Marmarelis, 1978). One of the most common approaches is to treat sensory neurons as filters whose outputs correspond to specific stimulus attributes in a scene. For example, neurons in primary visual cortex are often modeled as filters tuned to specific orientations and spatial frequencies (DeValois and DeValois, 1990). Often such models consider only a few critical stimulus attributes and ignore others. For computational simplicity, they often assume that stimuli are fixed and unchanging. However, even the simplest static visual stimulus can elicit a dynamic series of action potentials from visual neurons, and these responses can develop and persist over time. The simplest filter models fail to account for these complex temporal response dynamics.

Recent efforts have focused more closely on modeling responses to time-varying visual stimuli. One simple coding assumption that might reasonably account for the data is that neurons transmit information about time-varying stimuli by means of a temporally modulated rate code (for discussion of coding schemes, see Rieke et al. [1997]). According to this view, information is encoded in the instantaneous firing rate, and downstream neurons must estimate the instantaneous rate to decode the spike train. This process cannot be modeled in terms of a static filtering operation but requires a spatiotemporal filter sensitive to time-varying signals (Bialek et al., 1991; Theunissen et al., 2001; Vinje and Gallant, 1998).

While spatiotemporal filtering models have clear advantages over static filters, they also have limitations. Because real neurons transmit information via spike trains, they must simultaneously estimate the instantaneous firing rate of their inputs from a discrete series of spikes and translate their own time-varying state into a series of spikes for output to other cells. To resolve these decoding and encoding problems, modelers must consider the relationship between spatiotemporal filtering and the mechanisms governing spike generation. A model that produces realistic spike trains in response to a time-varying visual stimulus has the potential to substantially improve our understanding of neural coding.

Unfortunately, several practical problems have dissuaded researchers from constructing such models. Most importantly, many neurophysiological experiments have reported that action potentials are elicited unreliably and that their timing accuracy is poor (Shadlen and Newsome, 1998). In fact, these experiments have long been used to argue that single spikes are irrelevant and to justify simplifying assumptions (such as the mean-rate-code assumption described above). An additional complication stems from the spatiotemporal filtering framework itself: filtering is usually implemented as a quasilinear operation, but spiking is an inherently nonlinear process that requires a different modeling approach. Computational models for spike generation have been proposed (Gabbiani and Koch, 1998), but there has been relatively little work aimed at developing hybrid models that integrate a filter-based input stage with a realistic